REMARKS

This Reply is responsive to the Office Action dated September 10, 2002. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 1-13 were pending in this application at the time of the Office Action dated September 10, 2002. Claims 8 and 10-13 were withdrawn from consideration. As a result of this amendment, new claim 14 has been added. Accordingly, claims 1-7, 9 and 14 are now under examination.

II. Amendments to the Claims

Claim 1 was amended above to clarify that active fragments of the recited antibody have the same antigen binding activity. Support for this amendment may be found in the specification on page 8, lines 7-10. The term "thereof" was also replaced with the appropriate antecedent, and the terms "derivative" and "desired" were deleted. In addition, the optional requirement for a DNA sequence encoding a peptide sequence for targeting an antibody was deleted and moved to a newly submitted dependent claim, claim 14. Also, claim 1 was amended to include the positive process step of expressing the antibody or fragment or functional equivalent in the cellular compartment.

Claims 2-6 and 9 were amended to change "A" to "The" as suggested in the Office Action. Claims 2 and 4-6 were also amended to replace the term "derivative" with "functional equivalent" in order to maintain consistency with amended claim 1. Claim 9

was also amended to delete reference to non-elected claim 8, and to recite that the claimed seeds, fruits, progeny and hybrids contain the DNA sequence encoding the heavy chain immunoglobulin or fragment or functional equivalent thereof.

New claim 14 was added that provides that the DNA sequence recited in claim 1 comprises an additional sequence encoding a peptide sequence capable of targeting said antibody or fragment or functional equivalent thereof, to said cellular compartment. As mentioned above, support for this claim may be found in original claim 1.

No prohibited new matter has been added by way of these amendments.

III. Claim Objections

Claim 9 was objected to for depending on a claim directed to a non-elected invention. Claim 9 was amended above to delete reference to claim 8, accordingly the objection should now be withdrawn.

IV. Rejections Under 35 U.S.C. §112

Claim 9 was rejected under 35 U.S.C. §112, first paragraph for lack of written description. According to the Office Action, the claim is drawn to progeny and hybrid plants having undisclosed identifying characteristics. Claim 9 has been amended above to recite that the claimed seeds, fruits, progeny and hybrids contain the DNA encoding a heavy chain immunoglobulin or active fragment or derivative thereof as defined in earlier claims. Accordingly, the rejection of claim 9 under 35 U.S.C. §112, first paragraph, should now be withdrawn.

Claims 1-7 and 9 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. These rejections will be addressed in the order presented in the Office Action for the Examiner's convenience.

Claims 1, 2, 4 and 5 were said to be indefinite in the recitation of "active fragment or derivative thereof." Specifically, it is allegedly unclear what activity is intended and what features would be retained by a "derived" product. In addition, it is allegedly unclear to which product "thereof" refers. Claim 1 was amended above to delete the term "derivative," and to clarify that active fragments and functional equivalents possess the antigen binding activity of the antibody. In addition, the term "thereof" in claim 1 was replaced with the appropriate antecedent. Accordingly, these rejections as to claim 1 should now be withdrawn.

In claims 2 and 4-6, the term "derivative" was replaced with "functional equivalent" to maintain consistency with claim 1. Applicants believe that it is clear in the context of amended claim 1, on which claim 2 depends, that the term "thereof" in claim 2 refers to the immunoglobulin and not the DNA sequence. Accordingly, these rejections as to claims 2, 4 and 5 should now be withdrawn.

Claim 1 was also rejected because of the recitation of a "desired" cellular compartment. Claim 1 was amended above to delete the word "desired." Accordingly, this rejection should now be withdrawn.

Claim 1 was also rejected because of the phrase "functionally equivalent thereto," because it is allegedly unclear what type of functional equivalence is intended and what the protein is functionally equivalent to. Applicants respectfully note that the term "functionally equivalent" is defined at page 8, lines 23-26, as meaning any protein or

fragment which as the same or similar antigen-binding properties, where said antigen-binding capacity is located in a single binding domain. Further, claim 1 was amended above to replace the term "thereto" with the appropriate antecedent. Accordingly, these rejections as to claim 1 should now be withdrawn.

Claim 1 was also rejected for the phrase "as appropriate." Claim 1 was amended above to delete this phrase, and to delete reference to a peptide sequence capable of targeting an antibody to a cell compartment (which is now the subject of dependent claim 14). Accordingly, this rejection as to claim 1 should now be withdrawn.

Claim 1 was also rejected for allegedly omitting the essential step of expressing an antibody. Claim 1 was amended above to include the step of expressing the antibody or active fragment or functional equivalent. Accordingly, this rejection should now be withdrawn.

Claim 2 was rejected for the phrase "obtainable from camelids" because it is unclear what is obtainable from camelids, *i.e.*, the antibody, the fragment or the functional derivative or all three. Claim 2 was also rejected because of the word "obtainable," which the Office Action suggests should be replaced with the word "obtained." Applicants respectfully submit that it is clear from the claim language that it is the DNA sequence that is obtainable from camelids. This is also clear from the specification, *i.e.*, Example 1. Further, Applicants respectfully decline the suggestion to replace "obtainable" with "obtained," since a DNA sequence that is obtainable from camelids need not be obtained directly from camelids, *i.e.*, synthetic sequences based on camelid sequences may be used. Accordingly, reconsideration and withdrawal of these rejections as to claim 2 are respectfully requested.

Claims 2-6 were rejected because they referred to "a" method according to claim 1 rather than "the" method of claim 1. The claims have been amended to replace the word "a" with "the" as suggested in the Office Action. Accordingly, this rejection as to claims 2-6 should now be withdrawn.

Claim 4 was rejected because of the phrase "binds to a protein." According to the Office Action, it is unclear what binds to the protein. Applicants respectfully submit that it is clear from both the claim language and the specification that any of the three, *i.e.*, the heavy chain immunoglobulin, the fragment or the functional equivalent, may bind to a protein present in the plant. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 5 was rejected because of the phrase "binds to a plant or animal pathogen." According to the Office Action, it is not clear what binds to the plant or animal pathogen, and further, whether the binding is to a plant or a plant pathogen. Applicants respectfully submit that it is clear from both the claim language and the specification that any of the three, *i.e.*, the heavy chain immunoglobulin, the fragment or the functional equivalent, may bind to a plant or animal pathogen. Further, the claim has been amended above to clarify that binding occurs to a plant pathogen. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 6 was rejected because of the phrase "binds to a plant hormone or metabolite." According to the Office Action, it is not clear what binds to the plant hormone or metabolite, and further, whether the binding is to a plant metabolite or any metabolite. Applicants respectfully submit that it is clear from both the claim language and the specification that any of the three, *i.e.*, the heavy chain immunoglobulin, the

fragment or the functional equivalent, may bind to the plant hormone or metabolite. Further, the claim has been amended above to clarify that binding occurs to a plant metabolite. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 9 was rejected because of the indefinite article "a" before the phrase "plant according to claim 7 or 8." The Office Action suggested that the term "a" be replaced with "the." The suggestion in the Office Action has been adopted, as reflected in amended claim 9 above. Accordingly, withdrawal of the rejection is respectfully requested.

V. Rejections Under 35 U.S.C. §101

Claim 9 was rejected under 35 U.S.C. §101 because the claim is allegedly directed to non-statutory subject matter. According to the Office Action, the claim is drawn to progeny and hybrid plants that, due to Mendelian inheritance of genes, do not contain the recited DNA construct. Claim 9 has been amended above to recite that the claimed seeds, fruits, progeny and hybrids contain the DNA encoding a heavy chain immunoglobulin or active fragment or derivative thereof as defined in earlier claims. Accordingly, the rejection of claim 9 under 35 U.S.C. §101 should now be withdrawn.

VI. Prior Art Rejections

Claims 1, 3, 4, 7 and 9 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Owen *et al.* or Le Gall *et al.* Claims 1, 3 and 6-7 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Artsaenko *et al.* Claims 1 and 2 were

rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Casterman *et al.* Applicants respectfully traverse these prior art rejections.

Except for WO94/04678 by Casterman *et al.*, all of the cited prior art refers to production of scFv in plants. As noted in the Office Action, these molecules comprise a heavy chain and a light chain. Claim 1 has been amended above to indicate that the recited DNA sequence encodes a heavy chain immunoglobulin that is devoid of a variable light chain domain. Accordingly, neither Owen *et al.* nor Le Gall *et al.* nor Artsaenko *et al.* anticipate the claimed invention.

Further, none of these references renders obvious the claimed invention. Indeed, although for some applications, the expression of scFv in plants has been successfully demonstrated, their use shows several drawbacks which are described in the instant specification. In this regard, reference is made to pages17-18 of the application as filed. First, the amount of such antibodies in the cytoplasm is generally low, due to the problem of forming disulphide bonds needed for structural stability in a reducing environment. Second, accumulation of scFv may adversely affect the structure and function of the organelles in which they are expressed. And third, targeted expression, especially in the cytoplasm, is an existing need.

Applicants have surprisingly found that the claimed heavy chain immunoglobulins, devoid of light chains, overcome these drawbacks in that they are produced in high amounts, which may be controlled by a promoter and targeted to a desired compartment by inclusion of a signal sequence. These molecules maintain their antigen binding activity upon expression in a plant cellular compartment. Further, the claimed immunoglobulins do not require the formation of sulfide bonds for their activity,

which is a significant advantage over scFv molecules, which need disulphide bridges for their expression and activity and are not, or only to a very low level, formed under the reducing conditions which occur in many cellular compartments. Also, in view of Ma *et al.* in Science 268, 716-719 (1995) (cited in the specification at page 3, line 4) and the thesis of Vu, 1999 (cited in the specification at page 6, limes 8-9), the expression level and retained antigen binding activity of the molecules of the invention is quite unexpected.

None of the cited documents refers to the drawbacks as identified by the applicant. They merely show expression of scFv in plants and that some antigen binding activity may be retained. There is no hint at expression of the improved molecules according to the invention in plants. Although Casterman *et al.* mention briefly that the antibody molecules that they describe may be expressed in plants, they provide no guidance on how to obtain this expression and where the expression takes place. Certainly there is no disclosure on targeted expression in cellular compartments.

The §102(b) rejection of claims 1 and 2 in view of Casterman *et al.* is based on the general reference in Casterman to Hiatt *et al.* as disclosing specific promoters and signal peptides. Applicants respectfully submit that a mere reference to another article that teaches bits and pieces of items required to practice the claimed invention does not translate to an enabling disclosure for the cited reference. Indeed, according to MPEP 2131.01, extra references may be relied upon to show a primary reference contains an "enabled disclosure" when the claimed composition or machine is disclosed *identically* by the reference. *In re Samour*, 571 F.2d 559 (CCPA 1978), and *In re Donahue*, 766 F.2d 531 (Fed. Cir. 1985) (with emphasis). Furthermore, according to MPEP 2121.02,

when a prior art reference merely discloses the structure of a claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of the invention will be adequate to show inoperability. Accordingly, Applicants respectfully submit that Casterman *et al.* is not an enabling reference by the mere inclusion of a reference to Hiatt *et al.*, and therefore cannot be relied upon as a §102(b) reference.

Further, Applicants respectfully submit that there is no reason for the skilled person to rely on the combination of Casterman *et al.* and Hiatt *et al.* because there was no reasonable expectation of success in view of the difficulties demonstrated in the prior art. Indeed, in view of the disclosures of the above-referenced Ma *et al.* in Science and the Vu PhD thesis, the expression of heavy chain immunoglobulins in plants is not straightforward. Applicants were the first to accomplish expression of these specific molecules in plants and to identify the retained binding activity and possibility of targeted expression.

Based on the above remarks, Applicants respectfully submit that the cited documents do not anticipate or render obvious the claims as amended. Accordingly, reconsideration and withdrawal of all the rejections under §102 and §103(a) are respectfully requested.

Finally, claim 9 was rejected under 35 U.S.C. §102(b), or in the alternative, under 35 U.S.C. §103(a) as being allegedly anticipated by or obvious over Artsaenko *et al.* According to the Office Action, this rejection is based on the argument that there are insufficient identifying characteristics for the seeds, progeny, fruits and hybrids recited in claim 9. As discussed above, claim 9 was amended to indicate that the claimed seeds,

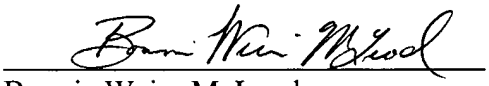
progeny, fruits and hybrids contain the recited DNA construct. Accordingly, this rejection may now be withdrawn.

This reply is fully responsive to the Office Action dated September 10, 2002. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
Morgan, Lewis & Bockius LLP



Bonnie Weiss McLeod
Registration No. 43,255

Dated: **March 10, 2003**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Ave., N.W.
Washington, D.C. 20004
202-739-3000
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APPENDIX

The following amendments were submitted above:

1. (Amended) A method for modifying a plant to produce an antibody or an active fragment of an antibody showing the antigen binding activity of the antibody [or derivative thereof,] or a protein functionally equivalent [thereto] to the antibody showing the antigen binding activity of the antibody in a [desired] cellular compartment, comprising introducing into a plant a DNA sequence encoding a heavy chain immunoglobulin devoid of a variable light chain domain, or an active fragment of said immunoglobulin, [or derivative thereof] or a sequence encoding a protein functionally equivalent [thereto] to the immunoglobulin, said DNA sequence being operably linked to one or more promoters, [and provided, as appropriate, with an additional sequence encoding a peptide sequence capable of targeting said antibody or fragment or derivative thereof, to said cellular compartment,] and expressing the antibody or fragment or protein functionally equivalent to the antibody, which are devoid of light chain domains but capable of specific binding with an antigen, in the cellular compartment.

2. (Amended) [A] The method according to claim 1 wherein the DNA sequence encoding the heavy chain immunoglobulin or fragment or [derivative] functional equivalent thereof is obtainable from camelids.

3. (Amended) [A] The method according to claim 1 or claim 2 wherein the plant is selected from tobacco, pea, potato, spinach, tomato or tea.

4. (Amended) [A] The method according to claim 1 wherein the heavy chain immunoglobulin or active fragment or [derivative] functional equivalent thereof binds to a protein present in the plant.

5. (Amended) [A] The method according to claim 1 wherein the heavy chain immunoglobulin or active fragment or [derivative] functional equivalent thereof binds to a plant pathogen or animal pathogen.

6. (Amended) [A] The method according to claim 1 wherein the heavy chain immunoglobulin or active fragment or [derivative] functional equivalent thereof binds to a plant hormone or plant metabolite.

9. (Amended) Seeds, fruits, progeny and hybrids of [a] the plant according to claim 7 [or 8] which comprise said DNA sequence encoding a heavy chain immunoglobulin or active fragment thereof or functional equivalent thereof.